Original Effective Date: 03/01/2018
Current Effective Date: 06/28/2025
Last P&T Approval/Version: 04/30/2025
Next Review Due By: 04/2026
Policy Number: C12651-A

Endari (L-glutamine) NC

PRODUCTS AFFECTED

Endari (L-glutamine), L-glutamine

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Sickle Cell Disease

REQUIRED MEDICAL INFORMATION:
All uses of Endari (L-glutamine oral powder) are considered not medically necessary for all indications, including but not limited to Sickle Cell Disease (SCD), due to insufficient evidence of therapeutic value since long term clinical benefit has not been established. Data from one clinical trial in a small number of people with SCD demonstrated fewer events than placebo group, but efficacy and clinical benefit, including effect on SCD outcomes and organ complications, has not been established. No long term data is available. This coverage policy is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Molina Healthcare will continue to evaluate and update this policy as relevant clinical evidence becomes available to determine whether Endari (L-glutamine oral powder) provides the impact on health outcomes or patient management.
Generic prescription hydroxyurea and over-the-counter (OTC), commercially available or powder for pharmaceutical compounding L-glutamine are available and recommended based on the limited evidence of Endari as discussed below. (Please see benefits for applicable coverage)

CONTINUATION OF THERAPY:
NA

DURATION OF APPROVAL:
NA

PRESCRIBER REQUIREMENTS:
NA

AGE RESTRICTIONS:
NA

QUANTITY:
NA

PLACE OF ADMINISTRATION:
NA

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Amino Acid

FDA-APPROVED USES:
Indicated to reduce the acute complications of sickle cell disease (SCD) in adult and pediatric patients 5 years of age and older.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Sickle cell disease (SCD) is a group of inherited red blood cell disorders.[3] Healthy red blood cells are round, and they move through small blood vessels to carry oxygen to all parts of the body.[3] In someone who has SCD, the red blood cells become hard and sticky and look like a C-shaped farm tool called a “sickle”.[3] The sickle cells die early, which causes a constant shortage of red blood cells.[3] Also, when they travel through small blood vessels, they get stuck and clog the blood flow.[3] This can cause pain and other serious problems such infection, acute chest syndrome and stroke.[3]
SCD affects millions of people worldwide and is most common in people with African heritage.[4] In the United States, about 100,000 Americans have SCD with a prevalence of 1 in 2,500 newborns, 1in 365 African Americans and 1 in 36,000 Hispanic births.[4] In the pathogenesis of SCD, the following are responsible for the various clinical manifestations: impaired circulation, destruction of RBCs, stasis of blood flow and

ongoing inflammatory responses.[4]
Administration of routine immunizations is crucial preventive care in managing SCD.[4] Impaired splenic function increases susceptibility to infection.[4] Children 6 months and older and adults with SCD should receive influenza vaccine annually.[4] Reduced mortality has been associated with the introduction of pneumococcal vaccines.[4] The risk of meningococcal disease is also higher in SCD and vaccination is recommended for individuals with functional or acquired asplenia.[4]
The only other available treatments have been hydroxyurea and chronic transfusions.[1] Hydroxyurea, which increases fetal hemoglobin levels, has reduced the number of painful crises (median 2.5/year vs 4.5/year with placebo), hospitalizations for sickle cell pain (median 1.0/year vs 2.4/year with placebo), and patients who required transfusions (median 48 vs 73 with placebo).[1] In a 17.5-year trial, it also appeared to improve survival without causing serious adverse effects.[1]
Endari (L-glutamine) is an amino acid indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older. FDA approval of Endari was based on the results of a48-week, double-blind trial, available only as an abstract, in 230 patients 5-58 years old with sickle cell anemia or sickle β-thalassemia who had experienced ≥2 painful crises within the past 12 months.[1] Patients were randomized to receive L-glutamine 0.3 g/kg or placebo twice daily; those who had been on stable doses of hydroxyurea for at least 3 months (about 66% in both groups) could continue taking it.[1] The median number of sickle cell crises during the 48 weeks of the trial, the primary endpoint, was 3 with L- glutamine versus 4 with placebo, a statistically significant difference.[1] Treatment with L-glutamine also reduced the median number of hospitalizations for sickle cell pain and increased the median time to first painful crisis.[1]

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
Contraindications to Endari (L-glutamine) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
The use of Endari (L-glutamine oral powder) is not covered for all indications due to insufficient evidence to establish clinical effectiveness or superiority over standard L-glutamine dietary supplements. There is no high-quality evidence and no head-to-head studies from published clinical trials and peer-reviewed literature evaluating the clinical safety and efficacy of this pharmaceutical grade L-glutamine oral powder versus over-the-counter L-glutamine, which is separately available as a nutritional supplement and widely available without a prescription at drugstores across the United States, although in much smaller doses than those the FDA recommends for sickle cell disease.

There is also limited evidence from published clinical trials and lack of data supporting the long-term benefits, side-effect profile, or risks associated with pharmaceutical grade L-glutamine (Endari) over the various L-glutamine dietary supplements. In addition, there is also no head-to-head studies with hydroxyurea, the only previous drug treatment available for the management of SCD. Hydroxyurea is the preferred agent in the treatment of SCD.

At this time, there are no guidelines relevant to L-glutamine (Endari) for SCD and no consensus from clinical experts to suggest that Endari is equivalent to or should replace hydroxyurea therapy. Currently, it may be considered as add-on therapy in patients ages 5 years and older who have at least two sickle cell crises a year, despite maximally tolerated hydroxyurea doses, or as monotherapy for patients unable to tolerate hydroxyurea.

Endari does not treat the underlying cause of SCD and has shown modest benefits in the reduction of sickle cell acute crisis (median 3 vs. median 4) and hospitalizations for sickle cell pain (median 2 vs. median 3). Furthermore, there are no head-to-head studies with hydroxyurea, the only previous drug treatment available for the management of SCD. At the present time, the role of Endari may be considered as add-on therapy since approximately two-thirds of the participants in both arms (63%) also had been receiving hydroxyurea on a stable dose for at least three months and continued

hydroxyurea during the pivotal phase 3 trial therefore, L-glutamine should not replace hydroxyurea therapy at this time.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Endari PACK 5GM
L-Glutamine PACK 5 GM

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable Revisions: Background References	Q2 2025
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2024
REVISION- Notable Revisions: Required Medical Information Place of Administration Other Special Considerations References	Q2 2023
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file